PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

B3

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
A61F 2/02, A61K 9/08

A2

(11) International Publication Number: WO 92/19182

(43) International Publication Date: 12 November 1992 (12.11.92)

(21) International Application Number: PCT/US92/03358

(22) International Filing Date: 23 April 1992 (23.04.92)

(30) Priority data:
690,849 24 April 1991 (24.04.91) US

(71) Applicant: BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM [US/US]; 201 West 7th Street, Austin, TX 78701 (US).

(72) Inventor: WILLERSON, James, T. ; 3314 Georgetown Road, Houston, TX 77225 (US).

(74) Agent: KITCHELL, Barbara, S.; Arnold, White & Durkee, P.O. Box 4433, Houston, TX 77210 (US).

(81) Designated States: AT, AT (European patent), AU, BB, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH, CH (European patent), CI (OAPI patent), CM (OAPI patent), CS, DE, DE (European patent), DK, DK (European patent), ES, ES (European patent), FI, FR (European patent), GA (OAPI patent), GB, GB (European patent), GN (OAPI patent), GR (European patent), HU, IT (European patent), JP, KP, KR, LK, LU, LU (European patent), MC (European patent), MG, ML (OAPI patent), MN, MR (OAPI patent), MW, NL, NL (European patent), NO, PL, RO, RU, SD, SE, SE (European patent), SN (OAPI patent), TD (OAPI patent), TG (OAPI patent).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: METHOD OF ATTENUATION OF NEOINTIMAL PROLIFERATION

(57) Abstract

The invention is a method of preventing or modulating neointimal proliferation in animals or humans following vascular injury. Treatment involves the use of two drugs, one a serotonin S_2 receptor antagonist and the other a dual thromboxane A_2 synthetase and receptor antagonist. The drugs are administered over a period of time, by bolus and continuous infusion.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FI	Finland	ML	Mali
AU	Australia	FR	France	MN	Mongolia
BB	Barbados	GA	Gabon	MR	Mauritania
BE	Belgium	GB	United Kingdom	MW	Malawi
BF	Burkina Faso	GN	Guinea	NL	Netherlands
BG	Bulgaria	GR	Greece	NO	Norway
BJ	Benin	HU	Hungary	PL	Poland
BR	Brazil	IE	Ireland	RO	Romania
CA	Canada	IT	Italy	RU	Russian Federation
CF	Central African Republic	JP	Japan	SD	Sudan
CG	Congo	KP	Democratic People's Republic of Korea	SE	Sweden
CH	Switzerland			SN	Senegal
CI	Côte d'Ivoire	KR	Republic of Korea	SU	Soviet Union
CM	Cameroon	LI	Liechtenstein	TD	Chad
CS	Czechoslovakia	LK	Sri Lanka	TG	Togo
DE	Germany	LU	Luxembourg	US	United States of America
DK	Denmark	MC	Monaco		
ES	Spain	MG	Madagascar		

METHOD OF ATTENUATION OF NEOINTIMAL PROLIFERATION

The invention relates to a method of treatment for inhibition or attenuation of neointimal proliferation associated with endothelial vascular injury. The method utilizes a combination of drugs which are administered over a period of time. This interferes with recurrent platelet aggregation that, without treatment, results in neointimal proliferation.

Acute coronary artery disease syndromes, including unstable angina pectoris and acute myocardial infarction, are speculated to be caused by the accumulation of platelet aggregates at sites of coronary artery stenosis and endothelial injury (1-4). Aggregating platelets release mediators that may promote further platelet aggregation, dynamic coronary artery vasoconstriction, and neointimal proliferation in the arterial wall (1,5-11). When coronary artery angioplasty is used as a treatment for focal atherosclerotic lesions, injury to the endothelium and media of the arterial wall occurs, and platelet aggregates form at these sites (12-16). It has been postulated that platelet aggregates accumulating at angioplasty sites may release factors that mediate a fibroproliferative response (1,3,15-18). A proliferative response of smooth muscle cells in the media and intima has been shown to cause the restenosis phenomenon after angioplasty (12-14,18).

Efforts have been focused on preventing or attenuating platelet activation through either the use of drugs or by preventing mechanical injury to the arteries. Such injury apparently occurs even with balloon dilatations, where the rate of recurrent stenosis after uncomplicated balloon dilatation is about 30% (19). This continues to be a significant problem despite continuing

efforts to develop new techniques and devices for angioplasty (20).

Various drugs have been used as treatments or prophylaxis of neointimal proliferation that leads to coronary artery stenosis after angioplasty and heart transplantation (21). These include general classes of organic compounds and drugs selected to target particular pathways thought to affect the processes involved in vascular occlusion. Interest in the role of thromboxane A_2 and 5-hydroxytryptophan (serotonin) in platelet activation has resulted in several animal studies using antagonists to these platelet activators. A combination of a thromboxane A_2 antagonist and a serotonin receptor antagonist has been shown to be effective in reducing residual intracoronary platelet deposition (22) observed at sites of coronary artery stenosis and endothelial injury after induced platelet activation (23).

The processes leading to neointimal proliferation after endothelial injury are incompletely understood. Platelet-derived growth factors (PDGF) as well as several other mitogens induce smooth muscle cell migration and proliferation (24-31). PDGFs are released from alpha granules of platelets following their activation and adhesion. On this basis, conventional wisdom has suggested that inhibition of platelet aggregation would be a logical step in preventing neointimal proliferation. Nevertheless, clinical use of antiplatelet agents such as aspirin has not prevented neointimal proliferation leading to restenosis after coronary angioplasty in patients with coronary artery disease (32). An effective treatment to prevent or attenuate neointimal proliferation commonly encountered following vascular surgery has not been available.

The present invention seeks to address a method to prevent or at least minimize the neointimal proliferation which frequently develops as a consequence of mechanical insult following surgical procedures involving major arteries. *In vivo* studies have shown that a combination of antiplatelet drugs, administered over a period of time following endothelial injury, will to a large degree prevent blood vessel constriction associated with neointimal proliferation.

Generally, the method of treatment involves administering a combination of drugs over a period of time. The drugs are antiplatelet agents and will be administered to a mammal or a human being which may have had an injury to the endothelium, either through surgical procedures or possibly from trauma such as accident or metabolic aberration.

Mechanical endothelial injury may commonly occur during surgical procedures. For example, angioplasty is a common surgical procedure used to clear arteries, damaged or impaired by deposits. Despite care in performing the procedures and despite new and better methods of performing these operations, mechanical injury to the vascular wall may occur. Injury, however small, to vascular walls results in platelet activation and over a period of time by processes incompletely understood, may lead to neointimal proliferation. That is, the endothelial cells within the cell walls will proliferate to the extent where blockage, sometimes completely occluding the vessel, is observed.

In the practice of this invention a combination of antiplatelet agents known to inhibit platelet activation are selected. Preferably two antiplatelet drugs are administered. One of these is selected from a group of

drugs with serotonin S_2 receptor antagonist activity. The other agent is selected from a group of drugs recognized as having thromboxane A_2 synthetase inhibitor activity. Most preferable drugs selected from this group have dual A_2 synthetase inhibitor activity as well as A_2 receptor antagonist activity. A preferred serotonin S_2 receptor antagonist is ketanserin. Several drugs having dual thromboxane A_2 synthetase inhibitor and receptor antagonist activity are also known, including ridogrel which is used in preferred practice.

Both antiplatelet agents should be administered when practicing this invention. Drugs need not be administered simultaneously but should be administered to the animal or human being receiving treatment either during surgery or shortly thereafter. In preferred practice, the antiplatelet agents are administered by bolus every 8 to 12 hrs and also by continuous infusion. Infusion should continue for 14 days but it is recognized that longer or shorter periods of continuous infusion may be indicated depending on the circumstances involved and the type of injury sustained. Where ketanserin is one of the drugs, preferred practice is administration of a 1 to 2 mg/kg bolus injection every 8 hrs with continuous infusion at .1 to .2 gm/kg/hr over a period of 14 days. The second antiplatelet agent preferably ridogrel is administered as a bolus at 5 to 10 mg/kg every 8 hrs and as a continuous infusion at 0.6 mg/kg/hr over a period of 14 days.

It should be recognized that methods of treatment may very depending on the type of injury sustained or the injury suspected as well as the physiological state of the patient. Thus it might be necessary to continue the treatment for periods as long as several months in order to prevent neointimal proliferation after treatment with

the drugs has ceased. Dosages and protocols for the regiment of administration may also be varied in accordance with the particular situations encountered.

It is also envisioned that this method of treatment would be effective when used to attenuate or prevent platelet aggregation in humans undergoing surgical procedures with risk of coronary stenosis. Other surgical procedures with a similar risk include stents, angioplasty, atherectomy, heart transplants, coronary bypass operations and laser procedures. Administration is preferably given prior to, during or immediately following the surgical procedure. However it is also envisioned that the drugs could be administered prophylactically prior to the surgery. A preferred drug combination is ridogrel and ketanserin administered by bolus and with continuous infusion. Administration of the drug should be continued for a period of time sufficient to attenuate or prevent neointimal proliferation.

Figure 1 is a representative coronary blood flow tracing from a dog on the fourth day after surgery to produce endothelial injury. SQ29548 (Squibb) is the thromboxane receptor antagonist.

Figure 2 shows histological changes within the left anterior descending coronary arteries (LAD) at 21 days after stenosis and endothelial injury. Neointimal proliferation (ip) is noticeable within the area indicated by the arrowheads. Panel A shows the LAD from a dog without cyclic flow variations (hematoxylin and eosin, x 60). Panel B shows LAD from a dog with frequent cyclic flow reductions in the first week after endothelial damage (hematoxylin and eosin, x 60). Panel C shows LAD from a dog with 1,321 cyclic flow reductions

in the first week following endothelial damage (hematoxylin and eosin, x 60).

Figure 3 shows the correlation between the frequency and severity of cyclic coronary flow velocity variations and the severity of coronary artery neointimal proliferation. Dogs (A) received ridogrel and ketanserin or LY53857 every 8 hrs in bolus doses for 7 to 14 days. Dogs (B) received ridogrel every 8 hrs in a bolus dose plus continuous infusions and ketanserin every 8 hrs plus continuous infusions for 14 days.

Materials and Methods

Animals

Mongrel dogs 17 to 34 kg of either gender were anesthetized with sodium pentobarbital (30 mg/kg intravenously) and ventilated with room air by a Harvard respirator (South Nadick, Massachusetts). Arterial and venous catheters were placed in a common carotid artery and a jugular vein for systemic arterial pressure measurements and administration of intravenous fluids or drugs, respectively.

Endothelial Injury

Anesthetized animals had a thoracotomy under sterile conditions. The left anterior descending (LAD) coronary artery was gently dissected free of surrounding tissues. A cylindrical pulsed-Doppler flow probe was placed around the exposed portion of the LAD and continuous recordings of LAD blood flow velocity were obtained. The arterial endothelium was injured by gently squeezing the external surface of the exposed artery with cushioned forceps. Next, a small plastic constrictor was placed around the

artery at the site of endothelial injury. The chest was closed. Following surgery, all animals were monitored closely with continuous recordings of LAD blood flow velocities and aortic blood pressures.

Ex Vivo Platelet Aggregation

Platelet aggregation was evaluated *ex vivo* in the experimental animals before applying the arterial constrictor and injuring the endothelium and each day during the period when treatments were given. Aggregation was determined using Born's method and the agonists ADP at a final concentration of 10-20 μM, U46619 (a thromboxane mimetic) at 50-100 ng/ml, and serotonin at 1-2 μM. Results of *in vitro* platelet aggregation studies were used to adjust *in vivo* dosages of the thromboxane A_2 and serotonin inhibitors given by sustained infusion in order to ensure complete abolition of *in vitro* responses to the platelet agonists due to *in vivo* infusion of the combined antagonists.

Histological Preparations

After animals were sacrificed, segments of the LAD and the circumflex coronary artery were dissected from the hearts, fixed in phosphate-buffered formalin, and embedded into paraffin. Histological sections were prepared. On photographic prints of the sections, structures were drawn onto the prints while examining the original slides by light microscopy. These areas were the media, original lumen (outlined by the inner edge of the media and delineated by the circumferential projection of the internal elastic lamella), area of intimal proliferation, and residual lumen. These areas were measured using a computer-linked digitizing tablet. The percent stenosis was calculated as:

$$(1 - \frac{\text{residual lumen area}}{\text{residual lumen + intima area}}) \times 100$$

EXAMPLE 1

Effect of Drug Treatment on Neointimal Proliferation

A total of 24 dogs were followed for 21 days. Seven of the dogs did not receive any treatment and served as controls. Another 17 dogs received the antiplatelet agents, ridogrel (a dual thromboxane A_2 synthetase inhibitor and thromboxane A_2 receptor antagonist, Janssen Pharmaceuticals, Beerse, Belgium) (33) and either ketanserin (a serotonin S_2 receptor antagonist, Janssen Pharmaceuticals, Beerse, Belgium) (34) or LY53857 (another serotonin receptor antagonist, Eli Lilly, Indianapolis, IN) (35). Of these antiplatelet agent-treated dogs, 7 received bolus doses of ridogrel at 5 mg/kg and either ketanserin at 0.5 mg/kg or LY53857 at 0.2 mg/kg bolus injections every 8-12 hrs for 7-14 days through catheters positioned in the left atrium. The remaining 10 dogs received ridogrel at 5-10 mg/kg every 8 hrs and a 0.6 mg/kg/hr continuous infusion and ketanserin as 1-2 mg/kg bolus injections every 8 hrs and a 0.1-0.2 mg/kg/hr continuous infusion for 14 days.

Coronary artery cyclic flow variations (CFVs) developed in 4 of the 7 non-treated dogs. CFVs also developed in 4 of the 17 dogs that received combined treatment with two antiplatelet agents, ridogrel and either ketanserin or LY53857. During the initial coronary flow recordings after surgery, most dogs had CFVs that disappeared in the subsequent 12 hrs. In the animals that developed CFVs later, they usually occurred during the second to fourth days following the surgical procedures. Figure 1 shows a typical coronary blood flow

tracing indicating a CFV in a dog 4 days after surgery to induce endothelial injury. The dog had been treated with the antiplatelet agent SQ29548 (Squibb), a thromboxane receptor antagonist, following surgery.

On the 21st day following surgery, animals were sacrificed with large doses of intravenous sodium pentobarbital. Histological examination of left anterior descending coronary artery tissues of animals that had received no drugs revealed various degrees of neointimal proliferation with modified smooth muscle cells present in the thickened intima of the LAD at sites of endothelial injury and arterial constriction (Fig. 2). Some vessels also showed evidence of organized thrombi. The original arterial lumen was determined by the internal elastic lamella or edge of the media where the internal elastic lamella is absent. As indicated in Figure 2, panel A, dogs without cyclic flow variations show minimal intimal proliferation while a dog with frequent cyclic flow reductions in the first week after endothelial damage had moderately severe intimal proliferation (Panel B of Figure 2). Severe intimal proliferation was observed in a dog with 1,321 cyclic flow reductions in the first week following endothelial damage (Figure 2, Panel C).

Histological changes in the left anterior descending coronary arteries were also examined in dogs 21 days after endothelial injury and treatment with ridogrel and ketanserin. In a dog receiving 5 mg/kg ridogrel and ketanserin 0.5 mg/kg every 8 hrs for 14 days, 42% arterial lumen stenosis caused by neointimal proliferation was observed. On the other hand, minimal neointimal proliferation was observed in a dog receiving ridogrel at 5 mg/kg every 8 hrs with 0.6 mg/kg/hr

continuous infusion and ketanserin at 1 mg/kg every 8 hrs with 0.1 mg/kg/hr continuous infusion for 2 weeks.

The severity of neointimal proliferation was related to the frequency and severity of CFVs (Fig. 3). In the 6 dogs with severe CFVs defined as more than 9 flow reductions greater than 70% of baseline flow velocity values during the first week following surgery, the LAD lumens were narrowed 84±5% (mean ± S.E.) by neointimal proliferation and/or organizing thrombi. In 2 dogs with mild to moderate CFVs, defined as more than 3 flow reductions that were 30-60% of baseline flow velocity levels, neointimal proliferation resulted in 40±5% narrowing of the LAD lumen. In the remaining animals without CFVs, only 17±4% narrowing of the LAD lumen by neointimal proliferation was observed. The correlation between the severity and frequency of CFVs and the severity of neointimal proliferation was significant ($r = 0.90$, $p \leq 0.001$) (Fig. 3).

The present invention has been described in terms of particular embodiments found by the inventor to comprise preferred modes of practicing the invention. It will be appreciated by those of skill in the art that in light of the present disclosure numerous modifications and changes can be made in the particular embodiments exemplified without departing from the proper scope of the invention. For example, other antiplatelet drugs could be combined with the combination of the present invention or prophylactic therapy could be developed as standard protocol prior to any surgical procedure with potential mechanical endothelial vascular damage. The mode of practice described could be altered, for example, intermittent infusions with or without periodic bolus administration. These and obvious related modifications are contemplated to be within the scope of the claims.

REFERENCES

The references listed below are incorporated herein by reference to the extent they supplement, explain, provide a background or teach methodology, techniques and/or compositions employed herein.

1. Willerson, J.T., Golino, P., Eidt, J., Campbell, W.G. & Buja, L.M. (1989) Circulation, Vol. 80, 198-205.

2. Willerson, J.T., Campbell, W.B., Winniford, M.D., Schmitz, J., April, P., Firth, B.G., Ashton, J., Smitherman, T., Bush, L. & Buja, L.M. (1984) Am. J. Cardiol., Vol. 54, 1349-1354.

3. Ross, R. (1986) N. Engl. J. Med., Vol. 314, 488-500.

4. Davies, J.J., Woolf, N., Rowles, P.M. & Pepper, J. (1988) Br. Heart J., Vol. 60, 459-464.

5. Golino, P., Ashton, J.H., Buja, L.M., Rosolowsky, M., Taylor, A.L., McNatt, J., Campbell, W.B. & Willerson, J.T. (1989) Circulation, Vol. 79, 154-166.

6. Clowes, A.W., Reidy, M.A. & Clowes, M.M. (1983) Lab Invest., Vol. 49, 208-215.

7. Harker, L.A., Harlan, J.J. & Ross, R. (1983) Circ. Res., Vol. 53, 731-739.

8. Reidy, M.A. (1988) Lab. Invest., Vol. 59, 36-43.

9. Tada, T., Reidy, M.A. (1987) Am. J. Path., Vol. 129, 429-433.

10. Clowes, A.W., Reidy, M.A. (1987) Am. J. Path., Vol. 516, 673-678.

11. Sprugel, K.H., McPherson, J.M., Clowes, A.W., Ross, R. (1987) Am. J. Path., Vol. 129, 601-613.

12. Liu, M.W., Roubin, G.S. & King, S.B. (1989) Circulation, Vol. 79, 1374-1387.

13. Block, P.C., Myler, P.K., Stertzer, S. & Fallon, J.T. (1981) N. Engl. J. Med., Vol. 305, 382-385.

14. Uchida, Y., Kawamura, K., Shibuya, I. & Hasegawa, K. (1988) Circulation, Vol. 78 (suppl. II), II-84.

15. Faxon, D.P., Sanborn, T.A., Weber, V.J., Haudenschild, C., Gittsman, S.B., McGovern, W.A. & Ryan, T.J. (1984) Arteriosclerosis, Vol. 4, 189-195.

16. Anderson, H.V., Yao, S., Murphree, S.S., Buja, L.M., McNatt, J.M., Willerson, J.T. (1990) Coronary Artery Disease, Vol. 1, 717-723.

17. Essed, C.E., van den Brand, M. & Becker, A.E. (1983) Br. Heart J., Vol. 49, 393-396.

18. Austin, G.E., Ratliff, N.B., Hollman, J., Tabei, S. & Phillips, D.F. (1985) J. Am. Coll. Card., Vol. 6, 369-375.

19. Sigwart, U., Herz(GER) 15, 319-328 (1990).

20. U.S. Patent No. 4,921,482, May 1, 1990.

21. Berthold and Payne, U.S. Patent No. 4,322,437, March 30, 1982.

22. Golino et al., Circulation 78, 701-711 (1988).

23. Golino et al., Circulation 79, 911-919 (1989).

24. Ross, R., Raines, E.W. & Bowen-Pope, D.F. (1986) Cell, Vol. 46, 155-169.

25. Raines, E.W., Dower, S.K. & Ross, R. (1989) Science, Vol. 243, 393-396.

26. Geisterfer, A.A., Peach, M.J. & Owens, G.K. (1988) Circ. Res., Vol. 62, 749-756.

27. Shuman, M.A. (1986) Ann. NY Acad. Sci., Vol. 485, 228-292.

28. Hansson, G.K., Jonasson, L., Lojsthed, B., Stemme, S., Kocher, O. & Gabbiai, G. (1988) Atherosclerosis, Vol. 72, 135-141.

29. Klagsbrun, M. & Edelman, E.R. (1989) Arteriosclerosis, Vol. 9, 269-278.

30. Roberts, A.B., Sporn, M.B., Asoian, R.K., Smith, J.M., Roche, N.S., Wakefield, L.M., Heine, U.I., Liotta, L.A., Falanga, V., Kehrl, J.H. & Fauci, A.S. (1986) Proc. Natl. Acad. Sci. U.S.A., Vol. 83, 4167-4171.

31. Wilcox, J.N., Smith, K.M., Williams, L.T., Schwartz, S.M. & Gordon, D. (1988) J. Clin. Invest., Vol. 82, 1134-1143.

32. Council on Scientific Affairs, AMA. (1984) JAMA, Vol. 251, 764-768.

33. DeClerck, F., Beetens, J., de Chaffoy de Courcelles, D., Freyne, E. and Janssen, P.A.J., Thromb. Heemosta. 61, 35-42 (1989).

34. DeClerck, F., David, J. and Janssen, P.A.J., Agents Actions 12, 388-397 (1982).

35. Cohen, M.L., fuller, R.W. and Kurz, K.D., J. Pharm. Exp. Ther. 227, 327-332 (1983).

CLAIMS:

1. A method of preventing or attenuating neointimal proliferation following vascular endothelial injury, comprising administering over a period of time to a mammal known or suspected of having an endothelial injury, an effective amount of a pharmaceutically suitable preparation comprising at least two antiplatelet agents.

2. The method of claim 1 wherein one antiplatelet agent is selected from a group of drugs having serotonin S_2 receptor antagonist activity.

3. The method of claim 1 wherein the other antiplatelet agent is selected from a group of drugs having dual thromboxane A_2 synthetase inhibitor and thromboxane A_2 receptor antagonist activity.

4. The method of claim 1 wherein the antiplatelet agents are administered separately or in combination.

5. The method of claim 4 wherein the administration is by periodic bolus administration.

6. The method of claim 4 wherein the administration is by continuous infusion.

7. The method of claim 4 wherein the antiplatelet agents are administered by bolus every 8-12 hrs and by continuous infusion for 14 days.

9. The method of claim 1 wherein the vascular endothelial injury is mechanically induced.

9. The method of claim 2 wherein the antiplatelet agent having serotonin S_2 receptor antagonist activity is ketanserin.

10. The method of claim 9 wherein the ketanserin is administered as a 1-2mg/kg bolus injection every 8 hrs and as a continuous infusion for 14 days at 0.1-0.2 gm/kg/hr.

11. The method of claim 2 wherein the antiplatelet agent having serotonin S_2 receptor antagonist activity is LY53857.

12. The method of claim 3 wherein the antiplatelet agent having dual thromboxane A_2 synthetase inhibitor and thromboxane A_2 receptor antagonist activity is ridogrel.

13. The method of claim 12 wherein the ridogrel is administered as a bolus at 5-10 mg/kg every 8 hrs and as a continuous infusion for 14 days at 0.6 mg.kg/hr.

14. The method of claim 1 wherein the mammal is a human.

15. A method of preventing or attenuating recurrent platelet aggregation and dislodgement in a mammal undergoing a surgical procedure with a risk of coronary stenosis comprising administering to said mammal an effective amount of a first agent having serotonin S_2 receptor antagonist activity and a second agent having dual thromboxane A_2 synthetase inhibitor and thromboxane A_2 receptor antagonist activity.

16. The method of claim 15 wherein the mammal is a human.

17. The method of claim 15 wherein the administering is prior to the surgical procedure.

18. The method of claim 15 wherein the administering is during or immediately following the surgical procedure.

19. The method of claim 15 wherein first agent is LY53857 or ketanserin.

20. The method of claim 15 wherein the second agent is ridogrel.

21. The method of claim 15 wherein the surgical procedure with a risk of coronary stenosis is stents, angioplasty, coronary bypass, heart transplant or atherectomy.

22. The method of claim 15 wherein the first agent and the second agent are administered by bolus and continuous infusion for a period of time sufficient to attenuate or prevent the neointimal proliferation.

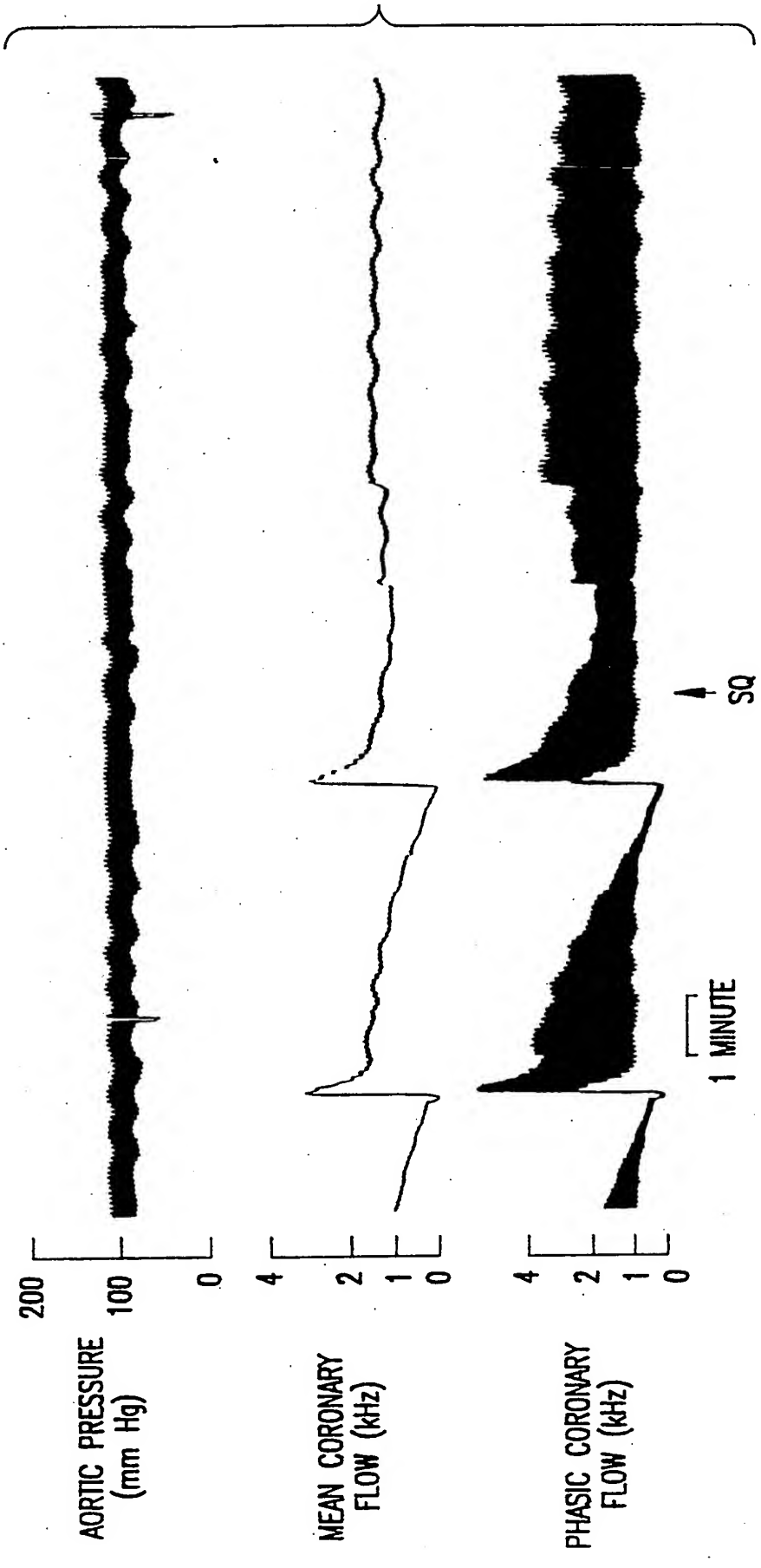
AORTIC PRESSURE (mm Hg)
200
100
0
MEAN CORONARY FLOW (kHz)
4
2
1
0
PHASIC CORONARY FLOW (kHz)
4
2
1
0
SQ
1 MINUTE

FIG. 1

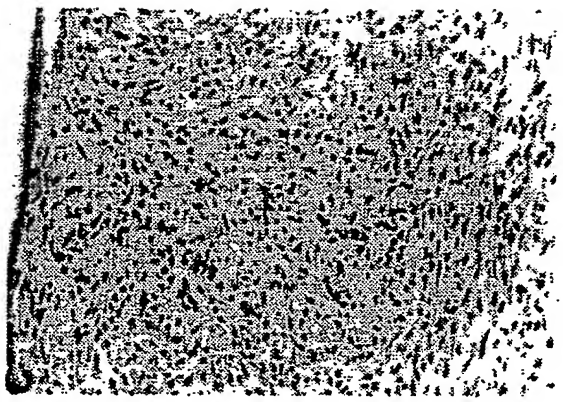

FIG. 2C

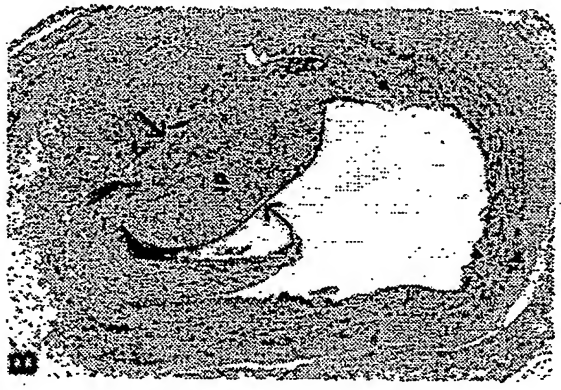

FIG. 2B

FIG. 2A

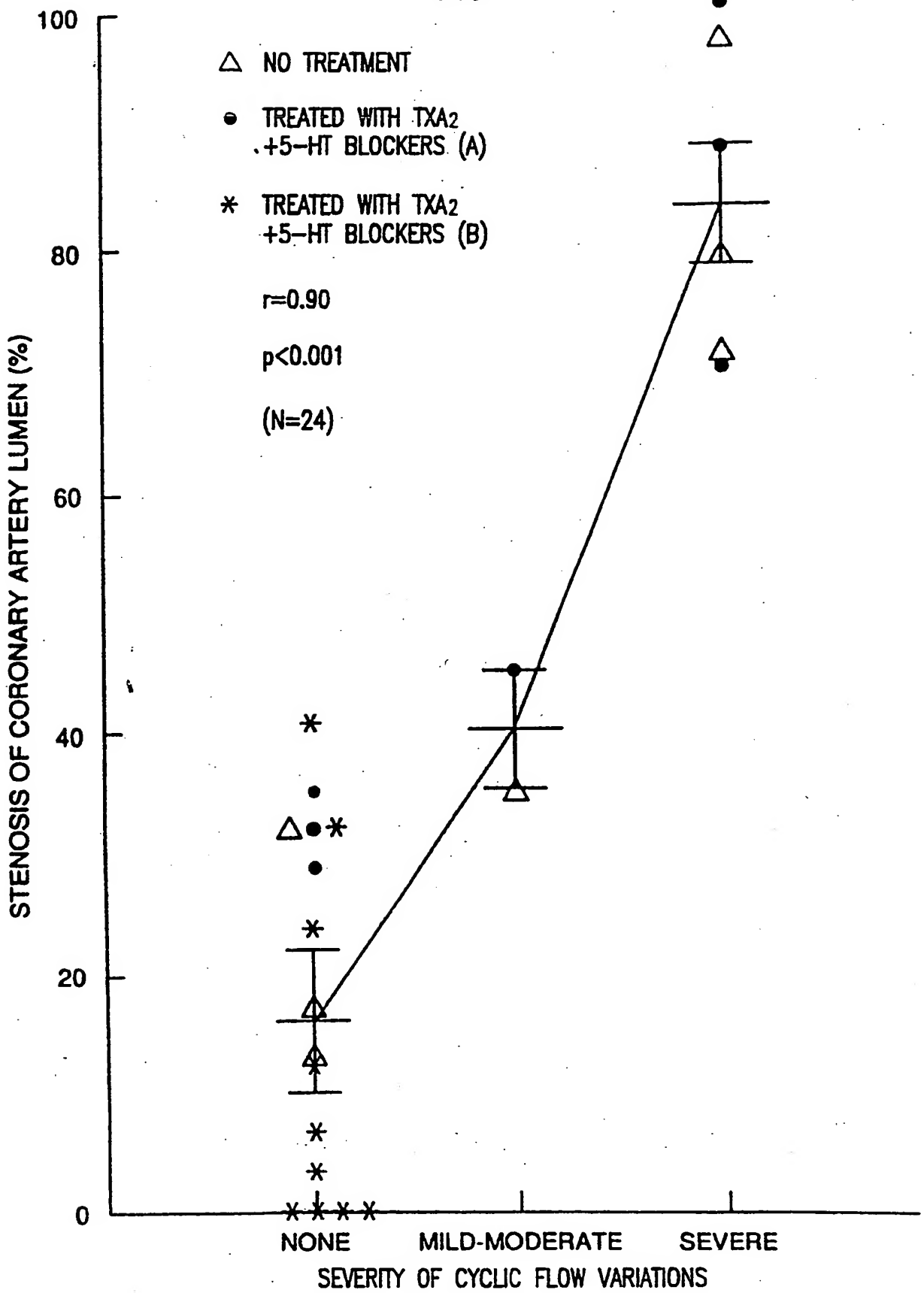
100
80
60
40
20
0
STENOSIS OF CORONARY ARTERY LUMEN (%)
△ NO TREATMENT
● TREATED WITH TXA2 +5-HT BLOCKERS (A)
* TREATED WITH TXA2 +5-HT BLOCKERS (B)
r=0.90
p<0.001
(N=24)
NONE
MILD-MODERATE
SEVERE
SEVERITY OF CYCLIC FLOW VARIATIONS

FIG. 3